

DATA SHEET

ELIDEL[®] **Pimecrolimus** **1% Cream**

Qualitative and quantitative composition

One gram of cream contains 10 mg of pimecrolimus.

For a full list of excipients, see List of excipients.

Pharmaceutical form

Cream for cutaneous use.

The cream is whitish, odourless, non-staining, and easily spreadable.

Clinical particulars

Therapeutic indications

Patients 3 months of age and older with atopic dermatitis (eczema) for the:

- short-term treatment of signs and symptoms; and
- intermittent long-term treatment of emerging and resolving lesions in atopic dermatitis where topical corticosteroids are ineffective, intolerable or inappropriate.

Dosage and method of administration

Apply a thin layer of Elidel 1% cream to the affected skin twice daily and rub in gently and completely.

Elidel 1% cream may be used on all skin areas, including the head and face, neck and intertriginous areas except on mucous membranes. Elidel 1% cream should not be applied under occlusive dressings.

Emollients are considered maintenance therapy for patients with atopic dermatitis (eczema).

In the intermittent long-term management of atopic dermatitis (eczema), Elidel 1% cream treatment should begin at first appearance of signs and symptoms of atopic dermatitis to prevent flares of the disease. Elidel 1% cream should be used twice daily until signs and symptoms resolve. In general, the duration of treatment with Elidel 1% cream for each eczema episode should not exceed 6 weeks (also see 'Use in paediatric patients'). If signs and symptoms persist beyond 6 weeks, or the condition worsens, Elidel 1% cream should be stopped and patients should be re-examined to confirm the diagnosis of atopic dermatitis, Treatment should be discontinued when there is no longer evidence of the disease apart from dry skin. Treatment can be resumed upon first recurrence of signs and symptoms to prevent flares of the disease.

If the patient is not well controlled on Elidel cream and emollients alone, a short course of a topical mid-potency corticosteroid can be used. Once the flare is under control, the patient can resume using Elidel cream and emollients as outlined above.

Emollients can be applied immediately after using Elidel 1% cream. However, after a bath/shower, emollients should be applied before using Elidel 1% cream.

Long-term continuous use of Elidel 1% cream is not recommended. Therapy should be intermittent, in conjunction with other therapies.

Use in paediatric patients

Use of this product is for children three months-of-age and above. Use in babies under three months-of-age has not been evaluated.

In the absence of safety data beyond 12 months duration, use of Elidel 1% cream in infants (3-23 months-of-age) should be limited to the smallest practicable body surface area and treatment of each episode should generally be limited to no more than 3 weeks.

For children (2 to 11 years), and adolescents (12 to 17 years) the dosing recommendation is the same as for adults.

Use in babies under 3 months of age has not been evaluated.

Use in the elderly

Atopic dermatitis (eczema) is rarely observed in patients aged 65 and over. Clinical studies with Elidel 1% cream did not include a sufficient number of patients in this age range to determine whether they respond differently from younger patients.

Contraindications

Known hypersensitivity to pimecrolimus or to any of the excipients (see List of excipients).

Special warnings and precautions for use

Long-term safety of Elidel 1% cream has not been established.

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including Elidel 1% cream (see Adverse effects).

As the long-term effect on the local skin immune response and on the incidence of skin malignancies is unknown, Elidel 1% cream should not be applied to potentially malignant or pre-malignant skin lesions.

Elidel 1% cream should not be applied to areas affected by acute cutaneous viral infections.

In the presence of a dermatological bacterial or fungal infection, the use of an appropriate antimicrobial agent should be instituted. If resolution of the infection does not occur, Elidel 1% cream should be discontinued until the infection has been adequately controlled.

The safety of Elidel 1% cream has not been established in patients with Netherton's syndrome and generalised erythroderma. Elidel 1% cream is not recommended in patients with Netherton's syndrome or severely inflamed or damaged skin (e.g. erythroderma) where there is a potential for increased absorption.

The safety and efficacy of Elidel 1% cream in immunocompromised patients have not been studied. The use in immunocompromised patients is therefore not recommended.

In clinical studies, 14/1,544 (0.9%) cases of lymphadenopathy were reported while using Elidel 1% cream. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear etiology or were known to resolve. Patients who receive Elidel 1% cream and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, Elidel 1% cream should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Throughout the course of treatment, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure. The potential effects of Elidel 1% Cream on skin response to ultraviolet damage are not known (see Preclinical safety data).

Use of Elidel 1% cream may cause mild and transient reactions at the site of application, such as a feeling of warmth and/or burning sensation. Patients should see a physician if an application site reaction is severe. In rare cases, application site reactions can be severe. Elidel should not be used on broken skin.

Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the cream should be thoroughly wiped off and rinsed off with water.

Interaction with other medicinal products and other forms of interaction

Potential interactions between Elidel 1% cream and other drugs and the compatibility between Elidel and other topical preparations have not been systematically evaluated. Based on its minimal extent of absorption, interactions of Elidel 1% cream with systemically administered drugs are unlikely to occur (see Pharmacokinetic properties).

A study that included 79 infants treated for up to 2 years showed that treatment with Elidel 1% Cream did not interfere with the protective immune response to childhood vaccinations. Application of Elidel 1% cream to vaccination sites, as long as local reactions persist, was not studied and is therefore not recommended.

Pregnancy and lactation

Pregnancy

There are no adequate data from the use of Elidel 1% cream in pregnant women. Animal studies using dermal application do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see Preclinical safety data).

Caution should be exercised when prescribing Elidel 1% cream to pregnant women. However, based on the minimal extent of pimecrolimus absorption after topical application of Elidel 1% cream (see Pharmacokinetic properties), the potential risk for humans is considered limited.

Lactation

Animal studies on milk excretion after topical application were not conducted. It is not known whether pimecrolimus is excreted in the milk after topical application. Because many drugs are excreted in human milk, caution should be exercised when Elidel 1% cream is administered to a nursing woman. However, based on the minimal extent of pimecrolimus absorption after topical application of Elidel 1% cream, (see Pharmacokinetic properties), the potential risk for humans is considered limited.

Nursing mothers should not apply Elidel 1% cream to the breast.

Fertility

There are no clinical data on the effects of pimecrolimus on male or female fertility (see Preclinical safety data).

Effects on ability to drive and use machines

Elidel 1% cream has no known effect on the ability to drive and use machines.

Adverse effects

The safety profile of Elidel 1% cream has been established in more than 2000 patients including infants (≥ 3 months), children, adolescents, and adults enrolled in phase 2 and 3 studies. Over 1500 of these patients were treated with Elidel 1% cream and over 500 were treated with control treatment i.e. either Elidel vehicle and/or topical corticosteroids.

The most common adverse events were application site reactions which were reported by approximately 19% of the patients treated with Elidel 1% cream and 16% of patients in the control group. These reactions generally occurred early in treatment, were mild/moderate in severity and were of short duration.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Table 1

Skin and subcutaneous tissue disorders	
Very common	application site burning
Common	application site reactions (irritation, pruritus and erythema), skin infections (folliculitis)
Uncommon	impetigo, condition aggravated, herpes simplex, herpes simplex dermatitis (eczema herpeticum), molluscum contagiosum, application site disorders such as rash, pain, paraesthesia, desquamation, dryness, oedema, skin papilloma, furuncle

The following adverse reactions have been reported during post-marketing experience. The frequency has been estimated from the reporting rates. Because these reactions are reported voluntarily from a population of uncertain size, the frequency reflects only an estimate.

Immune system disorders	
Very rare	anaphylactic reactions
Metabolism and nutrition disorders	
Rare	alcohol intolerance ¹⁾
Skin and subcutaneous tissue disorders	
Rare	allergic reactions (e.g. rash, urticaria, angioedema), skin discoloration (e.g. hypopigmentation, hyperpigmentation)

¹⁾ In most cases, flushing, rash, burning, itching or swelling occurred shortly after the intake of alcohol.

Rare cases of malignancy, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using pimecrolimus cream, although no causal relationship has been established (see Special warnings and precautions for use).

Overdose

There has been no experience of overdose with Elidel 1% cream.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatologicals, ATC code: D11AX15

Non-clinical pharmacology

Pimecrolimus is an anti-inflammatory ascomycin macrolactam derivative and a selective inhibitor of the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells.

Pimecrolimus binds with high affinity to macrophilin-12 and inhibits the calcium-dependent phosphatase calcineurin. As a consequence, it inhibits T cell proliferation and prevents the transcription and release of both T helper type 1 cell (TH1) and T helper type 2 cell (TH2) inflammatory cytokines such as interleukin-2, interferon-gamma, interleukin-4, interleukin-5, interleukin-10, tumor necrosis factor alpha and granulocyte macrophage colony-stimulating factor. Pimecrolimus and tacrolimus have similar potencies to inhibit recall antigen responses in human T-helper cell clones, isolated from the skin of an atopic dermatitis patient.

Pimecrolimus also prevents the release of cytokines and pro-inflammatory mediators from mast cells *in vitro* after stimulation by antigen/IgE. Pimecrolimus does not affect the growth of keratinocyte, fibroblast or endothelial cell lines and, in contrast to corticosteroids, does not impair the differentiation, maturation, functions and viability of murine Langerhans cells and human monocytes-derived dendritic cells, thus, underlining its cell-selective mode of action.

In studies using various topical formulations, including the pimecrolimus cream and tacrolimus ointment, pimecrolimus penetrates similarly into, but permeates less through skin *in vitro* than corticosteroids or tacrolimus, suggesting a lower systemic exposure to pimecrolimus after topical application as compared to tacrolimus and corticosteroids.

Pimecrolimus exhibits high anti-inflammatory activity in animal models of skin inflammation after topical and systemic application. Pimecrolimus is as effective as the high potency corticosteroids clobetasol-17-propionate and fluticasone after topical application in the pig model of allergic contact dermatitis (ACD). Topical pimecrolimus also inhibits the inflammatory response to irritants, as shown in murine models of irritant contact dermatitis. Furthermore, topical and oral pimecrolimus effectively reduces skin inflammation and pruritus and normalises histopathological changes in hypomagnesemic hairless rats, a model that mimics acute aspects of atopic dermatitis. Oral pimecrolimus is superior to cyclosporin A by a factor of 4 and superior to tacrolimus by a factor of more than 2 in inhibiting skin inflammation in ACD of rats.

Topical pimecrolimus does not cause skin atrophy in pigs, unlike clobetasol-17-propionate. Furthermore, pimecrolimus does not cause blanching and changes in skin texture in pigs, unlike clobetasol-17-propionate and fluticasone. Topical pimecrolimus does not affect epidermal Langerhans' cells in mice. In contrast, treatment with standard topical corticosteroids, including hydrocortisone, resulted in a reduction in Langerhans cells by 96 to 100%. A recent analysis of skin biopsies of atopic dermatitis patients has confirmed that treatment with the corticosteroid beta-methasone 0.1%, but not Elidel 1% cream, for 3 weeks results in depletion of Langerhans cells, while both drugs significantly reduce T cells. Thus, results from these as well as *in vitro* studies indicate that topically applied pimecrolimus is unlikely to interfere with the function of Langerhans/dendritic cells to differentiate naïve T cells into effector T cells, which is key for the developing immune system and maintenance of specific immunocompetence.

In contrast to its efficacy in skin inflammation models, the potential of pimecrolimus for affecting systemic immune responses is lower than that of tacrolimus and cyclosporin A, as shown in models of systemic immunosuppression and based on dose comparison. In the rat, after subcutaneous administration, the potency of pimecrolimus in inhibiting the formation of antibodies is 48-fold lower than with tacrolimus. Subcutaneous injections of cyclosporin A and

tacrolimus suppress the localized graft-versus-host reaction in rats 8-fold and 66-fold more potently than pimecrolimus. In contrast to cyclosporin A and tacrolimus, oral treatment of mice with pimecrolimus neither impairs the primary immune response nor decreases lymph node weight and cellularity in ACD.

The data show that topical pimecrolimus/Elidel has a high and selective anti-inflammatory activity in the skin and minimal percutaneous resorption. It differs from corticosteroids by its selective action on T cells and mast cells, by lack of impairment of Langerhans' cells/dendritic cells, by lack of induction of skin atrophy and by less permeation through skin. It differs from tacrolimus by less permeation through skin and by a lower potential for affecting systemic immune responses.

In animal safety pharmacology studies, single oral doses of pimecrolimus had no effect on basal lung and cardiovascular functions. CNS and endocrine parameters (e.g. GH, prolactin, LH, testosterone, corticosterone) were also unaffected. Based on its mechanism of action as a selective inhibitor of the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells, pimecrolimus is not expected to have any effect on the HPA axis.

Clinical data

Short-term (acute) treatment in paediatric patients

Children and adolescents: Two 6-week, vehicle-controlled trials were conducted including a total of 403 paediatric patients aged 2 to 17 years. Patients were treated twice daily with Elidel 1% cream. The data of both studies were pooled.

Infants: A similar 6-week study was conducted in 186 patients aged 3 to 23 months.

In these three 6-week studies, the efficacy results at endpoint were as follows:

Endpoint	Criteria	Children and adolescents			Infants		
		Elidel 1% (N=267)	Vehicle (N=136)	p-value	Elidel 1% (N=123)	Vehicle (N=63)	p-value
IGA*:	Clear or almost clear ¹	34.8%	18.4%	< 0.001	54.5%	23.8%	< 0.001
IGA*:	Improvement ²	59.9%	33%	not done	68%	40%	Not done
Pruritus:	Absent or mild	56.6%	33.8%	< 0.001	72.4%	33.3%	< 0.001
EASI ^o :	Overall (mean % change) ³	- 43.6	- 0.7	< 0.001	- 61.8	+ 7.35	< 0.001
EASI ^o :	Head/Neck (mean % change) ³	- 61.1	+ 0.6	< 0.001	- 74.0	+ 31.48	< 0.001

* Investigators Global Assessment
^o Eczema Area Severity Index (EASI) : mean % change in clinical signs (erythema, infiltration, excoriation, lichenification) and body surface area involved
¹: p-value based on CMH test stratified by centre
²Improvement=lower IGA than at baseline
³: p-value based on ANCOVA model of EASI at Day 43 endpoint, with centre and treatment as factors and baseline (Day 1) EASI a covariate;

A significant improvement in pruritus was observed within the first week of treatment in 44% of children and adolescents and in 70% of infants.

Long-term treatment in paediatric patients

In two double-blind studies of long-term management of atopic dermatitis in 713 children and adolescents (2 to 17 years) and 251 infants (3 to 23 months), Elidel 1% cream was evaluated as first line foundation therapy.

In addition to emollients, the Elidel group received Elidel 1% cream used at first signs of itching and redness to prevent progression to flares of atopic dermatitis. Only in case of flare not controlled by Elidel 1% cream, treatment with medium potency topical corticosteroids was initiated.

The control group received a standard treatment consisting of emollient plus medium potency topical corticosteroids to treat flares. Elidel vehicle was used instead of Elidel 1% cream in order to maintain the studies blind.

Both studies showed a reduction in the incidence of flares ($p < 0.001$) in favour of Elidel 1% cream first-line treatment; Elidel 1% cream first-line treatment showed better efficacy in all secondary assessments (Eczema Area Severity Index, IGA, subject assessment); pruritus was controlled within a week with Elidel 1% cream. Significantly more patients on Elidel 1% cream completed 6 months (children (61% Elidel 1% cream vs 34% control); infants (70% Elidel vs 33% control) and 12 months (children 51% Elidel vs 28% control) with no flare. Significantly more patients treated with Elidel 1% cream did not use corticosteroids in the first 6 months (children: 65% Elidel vs 37% control; infants: 70% Elidel vs 39% control) or 12 months (children: 57% Elidel 1% cream vs 32% control). The efficacy of Elidel 1% cream was maintained over time with the ability to prevent disease progression to severe flares.

Special studies

Tolerability studies demonstrated that Elidel 1% cream is devoid of any irritation, contact sensitising, phototoxic or photosensitising potential.

The atrophogenic potential of Elidel 1% cream in humans was tested in healthy volunteers treated for 4 weeks. As measured by echography, as compared to Elidel 1% cream and its vehicle, which did not induce a reduction of skin thickness.

Pharmacokinetic properties

Data in animals

Pimecrolimus is lipophilic. When applied topically its permeation through skin is very low. In minipigs, the total drug-related material systemically absorbed following a single 22 h application of Elidel 1% cream under semi-occlusion was at most 1% of the dose; the bioavailability of unchanged pimecrolimus was estimated to be about 0.03%. The amount of radiolabeled drug-related material in the skin at the application site remained essentially constant in the time interval 0 to 10 days after a 22-hour application; at 5 days post-dose, it represented almost exclusively unchanged pimecrolimus. The major fraction of the absorbed topical dose was completely metabolised and excreted slowly via the bile into the faeces.

Data in humans

Absorption in adults

Systemic exposure to pimecrolimus was investigated in 12 adult patients treated with Elidel 1% cream twice daily for 3 weeks. These patients had atopic dermatitis (eczema) lesions affecting 15 to 59% of their body surface area (BSA). 77.5% of pimecrolimus blood concentrations were below 0.5 ng/mL, the assay limit of quantitation (LoQ), and 99.8% of the total samples were below 1 ng/mL. The highest blood concentration of pimecrolimus measured in one patient was 1.4 ng/mL.

In 40 adult patients treated for up to 1 year with Elidel, having 14 to 62% of their BSA affected at baseline, 98% of pimecrolimus blood concentrations of pimecrolimus were consistently low, mostly below the LoQ. A maximum blood concentration of 0.8 ng/mL was measured in only 2 patients in week 6 of treatment. There was no increase in blood concentration over time in any patient during the 12 months of treatment. In 13 adult patients with hand dermatitis treated with Elidel twice daily for 3 weeks (palmar and dorsal surfaces of hands treated, overnight occlusion), the maximum blood concentration of pimecrolimus measured was 0.91 ng/mL.

Given the high proportion of pimecrolimus blood levels below the LoQ after topical application, the AUC could only be calculated from a few individuals. In 8 adult AD patients presenting with at least three quantifiable blood levels per visit day, the AUC_(0 to 12h) values ranged from 2.5 to 11.4 ng x h/mL.

Absorption in children

Systemic exposure to pimecrolimus was investigated in 58 paediatric patients aged 3 months to 14 years, who had atopic dermatitis (eczema) lesions involving 10 to 92% of the total body surface area. These children were treated with Elidel 1% cream twice daily for 3 weeks and five out of them were treated for up to 1 year on a "as needed" basis.

The blood concentrations measured in these paediatric patients were consistently low regardless of the extent of lesions treated or duration of therapy. They were in a range similar to that measured in adult patients treated under the same dosing regimen. 60% of pimecrolimus blood concentrations were below 0.5ng/mL (LoQ) and 97% of all samples were below 2 ng/mL. The highest blood concentrations measured in 2 paediatric patients aged 8 months to 14 years of age were 2.0 ng/mL.

In the youngest patients (aged 3 to 23 months), the highest blood concentration measured in one patient was 2.6 ng/mL. In the 5 children treated for 1 year, blood concentrations were consistently low, and the maximum blood concentration measured was 1.94 ng/mL (1 patient). In these five patients, there was no increase in blood concentration over time in any patient during the 12 months of treatment.

In 8 paediatric patients aged 2-14 years presenting at least three measurable blood concentrations per visit day, $AUC_{(0\text{ to }12\text{h})}$ ranged from 5.4 to 18.8 ng x h/mL. AUC ranges observed in patients with < 40% BSA affected at baseline were comparable to those in patients with $\geq 40\%$ BSA.

Comparison to oral PK Data

In psoriatic patients treated with oral pimecrolimus doses ranging from 5 mg once daily to 30 mg twice daily for 4 weeks, the drug was well tolerated at all doses including the highest dose. No significant adverse events were reported and no significant change was observed in physical examination, vital signs, and laboratory (including renal) safety parameters. The highest dose was associated with an $AUC_{(0\text{ to }12\text{h})}$ of 294.9 ng x h/mL. This exposure is approximately 26 and 16 times higher, respectively, than the highest systemic exposure observed in adult and paediatric atopic dermatitis (eczema) patients treated topically with Elidel twice daily for 3 weeks ($AUC_{(0\text{ to }12\text{h})}$ of 11.4 ng x h/mL and 18.8 ng x h/mL, respectively).

Distribution

Consistent with its skin selectivity, after topical application, pimecrolimus blood levels are very low. Therefore, pimecrolimus metabolism could not be determined after topical administration.

In vitro plasma protein binding studies have shown that 99.6% of pimecrolimus in plasma is bound to proteins. The major fraction of pimecrolimus in plasma is bound to different lipoproteins.

Metabolism

After single oral administration of radiolabeled pimecrolimus in healthy subjects, unchanged pimecrolimus was the major drug-related component in blood and there were numerous minor metabolites of moderate polarity that appeared to be products of O-demethylations and oxygenation.

No drug metabolism was observed in human skin *in vitro*.

Elimination

Drug-related radioactivity was excreted principally via the faeces (78.4%) and only a small fraction (2.5%) was recovered in urine. Total mean recovery of radioactivity was 80.9%. Parent compound was not detected in urine and less than 1% of radioactivity in faeces was accounted for by unchanged pimecrolimus.

Preclinical safety data

Toxicology studies after dermal application

A variety of preclinical safety studies were conducted with the pimecrolimus cream formulations in several animal species. There was no evidence of irritation, (photo) sensitisation, or local or systemic toxicity.

In a 2-year dermal carcinogenicity study in rats using Elidel 1% cream, no cutaneous or systemic carcinogenic effects were observed up to the highest practicable dose of

10 mg/kg/day or 110 mg/m²/day, represented by a mean AUC_(0 to 24h) of 125 ng x h/mL (equivalent to 3.3 times the maximum exposure observed in paediatric patients in clinical trials). In a mouse dermal carcinogenicity study using pimecrolimus in an ethanolic solution, no increase in incidence of neoplasms was observed in the skin or other organs up to the highest dose of 4 mg/kg/day or 12 mg/m²/day, corresponding to a mean AUC_(0 to 24h) value of 1,040 ng x h/mL (equivalent to 27 times the maximum exposure observed in paediatric patients in clinical trials).

In a dermal photocarcinogenicity study in hairless mice using Elidel 1% cream, no photocarcinogenic effect versus vehicle treated animals was noted up to the highest dose of 10 mg/kg/day or 30 mg/m²/day, corresponding to a mean AUC_(0-24h) value of 2,100 ng x h/mL (equivalent to 55 times the maximum exposure observed in pediatric patients in clinical trials).

In dermal reproduction studies, no maternal or fetal toxicity was observed up to the highest practicable doses tested, 10 mg/kg/day or 110 mg/m²/day in rats and 10 mg/kg/day or 36 mg/m²/day in rabbits. In rabbits, the corresponding mean AUC_(0 to 24h) was 24.8 ng x h/mL. AUC could not be calculated in rats.

Toxicology studies after oral administration

Adverse reactions not observed in clinical studies but seen in animals at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use, were as follows: reproduction studies in rats receiving oral doses up to 45 mg/kg/day or 490 mg/m²/day, corresponding to an extrapolated mean AUC_(0 to 24h) of 1448 ng x h/mL (equivalent to at least 63 times the maximum exposure observed in adult patients), revealed slight maternal toxicity, oestrus cycle disturbances, post-implantation loss and reduction in litter size.

An oral fertility and embryo-foetal developmental study in rats revealed estrus cycle disturbances, post-implantation loss and reduction in litter size at the 45 mg/kg/day dose (38 times the Maximum Recommended Human Dose (MRHD) based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (12 x MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23 x MRHD based on AUC comparisons), which was the highest dose tested in this study.

A second oral fertility and embryo-foetal developmental study in rats revealed reduced testicular and epididymal weights, reduced testicular sperm counts and motile sperm for males and estrus cycle disturbances, decreased corpora lutea, decreased implantations and viable fetuses for females at 45 mg/kg/day dose (123 x MRHD for males and 192 x MRHD for females based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (5 x MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 2 mg/kg/day (0.7 x MRHD based on AUC comparisons).

In an oral reproduction study in rabbits, maternal toxicity, but no embryotoxicity or teratogenicity was observed at the highest dose of 20 mg/kg/day or 72 mg/m²/day corresponding to an extrapolated mean AUC_(0 to 24h) value of 147 ng x h/mL (equivalent to at least 6 times the maximum exposure observed in adult patients).

In a mouse oral carcinogenicity study, a 13% higher incidence of lymphomas versus controls associated with signs of immunosuppression was observed at 45 mg/kg/day or 135 mg/m²/day, corresponding to a mean AUC_(0 to 24h) value of 9,821 ng x h/mL (equivalent to at least 258 times the maximum exposure observed in paediatric patients in clinical trials). A dose of 15 mg/kg/day or 45 mg/m²/day, corresponding to a mean AUC_(0 to 24h) value of 5,059 ng x h/mL, produced no lymphomas or discernible effects on the immune system (equivalent to 133 times the maximum exposure observed in paediatric patients in clinical trials). In an oral rat carcinogenicity study, no carcinogenic potential was observed up to a dose of 10 mg/kg/day or 110 mg/m²/day, exceeding the maximum tolerated dose, represented by a mean AUC_(0 to 24h) value of 1550 ng x h/mL (equivalent to 41 times the maximum exposure observed in pediatric patients in clinical trials).

Dose-dependent increases in the incidence of lymphomas were observed at all doses in a 39-week monkey oral toxicity study. Signs of recovery and/or at least partial reversibility of the effects were noted upon cessation of dosages in a few animals. Failure to derive a No Observed Adverse Effect Level (NOAEL) precludes an assessment of the margin of safety between a non-carcinogenic concentration in the monkey and exposures in patients. The systemic exposure at the Lowest Observed Adverse Effect Level (LOAEL) of 15mg/kg/day was 31 times the highest maximum exposure observed in a human (paediatric patient). The risk for humans cannot be ruled out as the potential for local immunosuppression with the long-term use of pimecrolimus cream is unknown.

A battery of *in vitro* and *in vivo* genotoxicity tests, including the Ames assay, mouse lymphoma L5178Y assay, chromosome aberration test in V79 Chinese hamster cells, and mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential of the drug.

Pharmaceutical particulars

List of excipients

Triglycerides, oleyl alcohol, propylene glycol, stearyl alcohol, cetyl alcohol, mono-and diglycerides, sodium cetostearyl sulphate, benzyl alcohol, citric acid, sodium hydroxide, purified water.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other topical medicinal products.

Emollients can be applied together with Elidel 1% cream (see Dosage and method of administration).

Shelf life

2 years. Once opened, the contents of the tube should be used within 1 year.

Special precautions for storage

Do not store above 25°C. Do not freeze.

Elidel 1% cream must be kept out of the reach and sight of children.

Nature and contents of container

Aluminium tube with an epoxy protective inner lacquer and polypropylene screw cap.

Tubes of 15 grams.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Medicine classification

Prescription Medicine

Name and address

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Date of preparation

8 June 2009
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